PETITION FOR HEALTH CLAIMS:

- CALCIUM AND CYCLIC SEVERE DEPRESSION ASSOCIATED WITH THE MENSTRUAL CYCLE.
- CALCIUM AND PREMENSTRUAL DYSPHORIC DISORDER.
- CALCIUM AND THE ONSENT OF SYMPTOMS OF PREMENSTRUAL DYSPHORIC DISORDER.
- CALCIUM AND ABNORMAL MENSTRUAL CYCLES.
- CALCIUM AND POLYCYSTIC OVARY SYNDROME.

SUBMITTED TO THE FOOD AND DRUG ADMINISTRATION
OCTOBER 9, 2003

PETITIONER:
MARINE BIO USA, INC.

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Attachments

October 9, 2003

PETITIONER: Marine Bio USA, Inc.

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SUBJECT: Petition for Health Claims:

1. Calcium may reduce the risk of cyclic severe depression associated with the menstrual cycle.
2. Calcium may reduce the risk of premenstrual dysphoric disorder.
3. Calcium may reduce the risk of the onsent of symptoms of premenstrual dysphoric disorder.
4. Calcium may reduce the risk of abnormal menstrual cycles.
5. Calcium may reduce the risk of polycystic ovary syndrome.

Food and Drug Administration
Office of Nutritional Products, Labeling, and Dietary Supplements
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I. Introduction and Statement of Purpose

The undersigned, Marine Bio USA, Inc. (hereinafter "Petitioner"), submits this petition pursuant to section 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act ("FDCA")(21 U.S.C. § 343(r)(5)(D)) with respect to calcium and (1) cyclic severe depression associated with the menstrual cycle; (2) premenstrual dysphoric disorder; (3) abnormal menstrual cycles; and (4) polycystic ovary syndrome. The proposed claims are contained in section D below. Attached hereto and constituting a part of this petition is all information necessary to satisfy the requirements in 21 C.F.R. § 101.70(f).

This petition presents a logical and valid evaluation of the scientific studies and clinical trials concerning the relationship between calcium and reduction in the risk of: cyclic severe depression associated with the menstrual cycle; premenstrual dysphoric disorder (PMDD); the

onset of symptoms of PMDD; abnormal menstrual cycles; and polycystic ovary syndrome (POS). The attached scientific studies demonstrate that the consumption of calcium may reduce the risk of cyclic severe depression associated with the menstrual cycle, premenstrual dysphoric disorder, the onset of symptoms of premenstrual dysphoric disorder, abnormal menstrual cycles and polycystic ovary syndrome. Those studies justify permitting health claims that link consumption of calcium with reduction in those risks. See Glade Report attached as Exhibit 1.

Calcium is the subject of an approved health claim for its relationship to osteoporosis. 21 C.F.R. § 101.72. As stated in the final rule for that health claim, ten forms of calcium have been shown to be safe and lawful for use in a dietary supplement to FDA's satisfaction in accordance with 101.14. 58 FR 2665, 2670 (Jan. 6, 1993)(calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate). Id. citing 56 FR at 60691. Thus, calcium is a safe and lawful substance and contributes nutritive value. 21 C.F.R. § 101.14(b)(i) and (ii). Similarly calcium is a substance within the meaning of 21 C.F.R. § 101.14(a)(2).

As discussed below, calcium possesses properties that have a multitude of beneficial effects in the body including reducing the risk of PMDD and POS. Thus, calcium is associated with the diseases that are the subject of this petition. 21 C.F.R. § 101.14(b)(i). The scientific report (Exhibit 1), the PDR for Nutritional Supplements chapter on calcium (Exhibit 2), the Institute of Medicine's chapter on calcium (Exhibit 3), and all of the attached scientific articles establish that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner consistent with generally recognized scientific procedures and principles), there is significant scientific agreement among experts qualified by

scientific training and experience to evaluate such claims, that calcium reduces the risk of cyclic severe depression associated with the menstrual cycle, PMDD, the onsent of symptoms of PMDD, abnormal menstrual cycles, and POS.

The scientific studies described in this petition directly address the important public health issues of the above-listed diseases. Those studies further national and DHHS policies by identifying low cost means of reducing risks of those diseases and disease conditions. The proposed health claims respond to major public health concerns in the United States.

Eighty percent of women are estimated to experience premenstrual syndrome (PMS), 40% of women (half of those experiencing PMS) experience symptoms sufficient to affect their daily lives, and 3% to 8% experience severe impairment from a disease state known as premenstrual dysphoric disorder (PMDD). Exhibit 1 at 4. Similarly, polycystic ovarian syndrome (POS) affects six to ten percent of reproductive-age women and is associated with an increased risk for diabetes mellitus, dyslipidemia, visceral obesity, hypertension and coronary artery calcification. Id. at 5.

The Petitioner believes that the truthful health information conveyed by its proposed succinct health claims will enable consumers to make prudent and effective dietary choices. Labeling dietary supplements with the proposed calcium claims will inform consumers at the point of sale of current scientific evidence concerning means to reduce the risks of the above-listed diseases and of health conditions that have a significant impact on the lives of women in the United States.

In accordance with FDA's July 10, 2003 "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" and consistent with the decision in Pearson v. Shalala, 164 F.3d. 650 (D.C.Cir. 1999), reh'g denied

en banc, 172 F.2d 72 (D.C.Cir. 1999); Pearson v. Shalala, 130 F.Supp.2d 105 (2001), recon. denied, Pearson v. Thompson, 141 F. Supp. 2d 105 (D.D.C. 2001); and Whitaker v. Thompson, 248 F. Supp. 2d 1 (D.D.C. 2002), the Petitioner respectfully requests that if the agency finds that any claim proposed does not satisfy its "significant scientific agreement" standard, that the agency authorize that claim, with such succinct and accurate disclaimers as are reasonably necessary to avoid a potentially misleading connotation.

A. Preliminary Requirements

1. Calcium meets the requirements of §101.14(b)

The proposed health claims meet the relevant eligibility requirements of 21 C.F.R. § 101.14(b). Section 101.14(b) requires:

> (b) Eligibility. For a substance to be eligible for a health claim:
>
> (1) the substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup (e.g., the elderly), is at risk, or, alternatively, the petition submitted by the proponent of the claim otherwise explains the prevalence of the disease or health-related condition in the U.S. population and the relevance of the claim in the context of the total daily diet and satisfies the other requirements of this section.
>
> (2) If the substance is to be consumed as a component of a conventional food at decreased dietary levels, the substance must be a nutrient listed in 21 U.S.C. 343(q)(1)(C) or (q)(1)(D), or one that the Food and Drug Administration (FDA) has required to be included in the label or labeling under 21 U.S.C. 343(q)(2)(A); or
>
> (3) If the substance is to be consumed at other than decreased dietary levels:
>
> (i) The substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in § 170.3(o) of this chapter, to the food and must retain that attribute when consumed at levels that are necessary to justify a claim; and
>
> (ii) The substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug and Cosmetic Act.

Calcium is eligible for a health claim. It currently is the subject of an approved health claim concerning its ability to reduce osteoporosis risk. 21 C.F.R. § 101.72.

a. Calcium is associated with a disease affecting the general U.S. population

A "disease or health-related condition" means "damage to an organ, part, structure, or system of the body such that it does not function properly (e.g. cardiovascular disease), or a state of health leading to such dysfunctioning (e.g. hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition (claims

pertaining to such diseases are thereby not subject to § 101.13 or § 101.70)." 21 C.F.R. § 101.14(a)(5).

The five health claims associate calcium with two diseases (PMDD and POS) and related health conditions (cyclic severe depression associated with the menstrual cycle and abnormal menstrual cycles). Those diseases and their related health conditions are ones for which the female US population is at risk. PMDD is a disease state of severe impairment associated with the menstrual cycle. Exhibit 1 at 4. Related to PMDD is premenstrual syndrome (PMS) referring to a cluster of mood, physical, and cognitive symptoms that occur with cyclic regularity in women in relation to their menstrual cycles. Those symptoms occur during the luteal phase of the human menstrual cycle and undergo spontaneous remission upon completion of the menses. Id. PMDD is a "severe disabling form of PMS." The National Women's Health Information Center[1] "Premenstrual Syndrome" http://www.4woman.gov/faq/pms.htm (last visited 8/19/2003), attached as Exhibit 4, at 2. The main symptoms of PMDD are mood disorders such as depression, anxiety, tension, and persistent anger or irritability that occur with severity and lead to problems with relationships and with performance of routine daily activities. Id. 80% of women are estimated to experience PMS syndrome and 40% of women (half of those experiencing PMS) experience symptoms sufficient to affect their daily lives. Exhibit 1 at 4. Three to eight percent of women experience PMDD.

Typical PMDD symptoms can be grouped as follows: affective symptoms (depression or sadness, irritability, tension, anxiety, tearfulness, restlessness, jitteriness, anger, loneliness, appetite change, food cravings, changes in the level of sexual interest), pain (headache, migraine, back pain, breast pain or tenderness, abdominal cramps, general muscular pain), cognitive or performance deficits (mood instability or mood swings, difficulty concentrating, decreased

[1] A project of the U.S. Department of Health and Human Services, Office on Women's Health.

mental efficiency, confusion, forgetfulness, social avoidance, clumsiness, carelessness, tantrums, hyperactivity), signs of fluid retention (breast swelling, weight gain, abdominal bloating or swelling, swelling of the extremities) and general somatic symptoms (fatigue, tiredness, dizziness, nausea, insomnia). Exhibit 1 at 4-5. PMDD may become debilitating. Id. at 5.

There are a variety of treatments for PMS, with none being universally effective. Exhibit 4 at 2. The HHS "4Women" publication on the topic recommends lifestyle changes including, "A calcium supplement with vitamin D can help keep bones strong and may help with PMS symptoms." Exhibit 4 at 2.

In polycystic ovary syndrome (POS) the ovaries are enlarged and have several fluid-filled sacs or cysts. National Women's Health Informaiton Center, "Polycystic Ovary Syndrome," http://www.4women.gov/faq/pcos.htm (last visited 8/19/2003), attached as Exhibit 5, at 1. Women with POS may experience a number of other symptoms in addition to having cysts on the ovaries. Id. POS is a leading cause of infertility and is the most common reproductive syndrome in women of childbearing age. Id. An estimate of six to ten percent of reproductive-age women (ages 20-40) have POS. Exhibit 1 at 5; see also Exhibit 5 at 1 (5-10%). At least 30% of women have some symptoms of POS. Exhibit 5 at 1. POS is characterized by hyperandrogenic chronic anovulation with infertility, theca cell hyperplasia, arrested follicular development, irregular menses, dysfunctional uterine bleeding, acanthosis nigricans, and hirsutism. Exhibit 1 at 5. Additional symptoms of POS include increased serum levels of male hormones; pelvic pain that lasts longer than six months; weight gain or obesity; high blood pressure; and acne, oily skin, or dandruff. Exhibit 5 at 2.

As with any disease, prevention is preferable to treatment. With POS, however, prevention is important as treatment is only through medication to control symptomology, rather

than the underlying disease, or through surgical intervention with minimal success. Most commonly birth control pills are prescribed to control POS symptoms. Id. Birth control pills regulate menstruation, reduce androgen levels, and help to clear acne. Id. Other drugs help with cosmetic problems while still others control blood pressure and cholesterol. Id. Progestins and insulin-sensitizing medications are taken to induce a menstrual period and restore normal cycles. Id. Finally, although not a first course of treatment, surgery called "ovarian drilling" is a treatment for POS in which laproscopy is used to enable a doctor to make punctures in the ovary to destroy a small portion of the ovary. Id. The success rate is less than 50% for ovarian drilling, and there is a risk of developing adhesions or scar tissue on the ovary. Id.

Thus, PMDD and POS are diseases and, along with their health-related conditions, are within the meaning of 21 C.F.R. § 101.14(a)(5). PMDD and POS affect the general female U.S. population. Moreover, prevention of both diseases is a significant issue for the female population in light of inadequate disease treatment options, particularly disease treatment options that avoid daily (perhaps even multiple) medication(s) and/or surgery.

b. Calcium contributes nutritive value at the levels present in supplements

In accordance with section 101.14(b)(3)(i), calcium contributes nutritive value. The Reference Daily Intake (RDI) for calcium is 1000 mg. 21 CFR § 101.9(b)(8)(iv).[2] The nutritive contribution of calcium is widely recognized. See generally, Exhibits 1, 2, and 3. FDA previously recognized calcium's nutritive value at the levels present in supplements in its final rule on the health claim concerning the relationship between calcium and osteoporosis. 56 FR 60689 at I.D.

[2] The Institute of Medicine recommends daily calcium intakes of 800 mg (4 through 8 years old), 1300 mg (9 through 18 years old), 1000 mg (19 through 50 years old) and 1200 mg (over 50 years old). Exhibit 1 at 51; Exhibit 3 at 91-117.

Calcium is an essential mineral that has a multitude of vital biological roles. Exh. 2 at 74; 56 FR 60689 at I.D. Calcium is, of course, a major constituent of bones and teeth. E.g., Exh. 2 at 74. In addition calcium is necessary for muscle contraction (including heart function), nerve conduction, blood coagulation, glandular secretion, energy production, and immune system function. Id. The mechanism of calcium's absorption, efficiency, and retention are discussed in detail in Exhibit 1. In addition to its anti-osteoporotic activity, calcium has anticarcinogenic activity. See Exh. 1 generally; Exh. 2 at 74-75; Exh. 3 at 89-91.

As stated in the Glade Report, there is an absolute lack of any reports of clinically-significant adverse reactions attributed to dietary calcium. Exhibit 1 at 8. The report goes on to state that the North American Menopause Society in its 2001 Consensus Opinion stated that the side effect profile from recommended levels of calcium intake is insignificant and that no serious side effects are associated with those levels. Id. Similarly the PDR reports that calcium supplements are generally well tolerated. Exhibit 2 at 77.

Calcium-containing supplements are available in different calcium salts (calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate) and in different forms (including capsules, chewable tablets, suspension, tablets, and wafers). 58 FR at 2670; Exhibit 2 at 77-78. Calcium supplements are available in a range of strengths from 150 mg to 1150 mg. Exh. 2 at 77-78.

c. Calcium is safe and lawful under the FDCA

"For each such ingredient listed, the petitioner should state how the ingredient complies with the requirements of § 101.14(b)(3)(ii), e.g., that its use is generally recognized as safe (GRAS), listed as a food additive, or authorized by a prior sanction issued by the agency, and

what the basis is for the GRAS claim, the food additive status, or prior sanctioned status." 21 C.F.R. § 101.70(f)(A). As stated in the final rule for the health claim concerning calcium and osteoporosis, calcium complies with the requirements of § 101.14(b)(3)(ii). Calcium has prior sanctioned status as safe and lawful under the FDCA.

The agency has determined that ten calcium compounds have been demonstrated to be safe and lawful for use in a dietary supplement: calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate. 58 FR at 2670 citing 56 FR at 60691.

In summary, since calcium meets the requirements in 21 C.F.R. § 101.14(b), the preliminary requirements of 21 C.F.R. § 101.70 are fully satisfied.

B. Summary of Scientific Data

1. Significant scientific agreement exists to support the proposed claims

There is significant scientific agreement among experts who study calcium and its effects on PMDD and POS that calcium is an effective modifier (reducer) of the risks of those diseases. Exhibit 1 at 1. Similarly there is significant scientific agreement that calcium is an effective modifier of the risks of abnormal menstrual cycles and of cyclic severe depression associated with the menstrual cycle. The scientific literature shows that calcium has a preventive effect on those diseases and their related health conditions. See Exhibit 1.

Dietary calcium deficiency is directly related to the symptoms of PMS and PMDD. Exhibit 1 at 9. Daily intakes of calcium meeting or exceeding the IOM's recommendations (DRIs) for calcium have been shown to produce beneficial effects upon reducing the development of symptoms associated with PMDD. Moreover, the presence of sufficient calcium is required to normalize the menstrual cycle. Id. Women with POS are characterized by irregular menstrual cycles. Daily intakes of calcium in excess of the DRI for calcium have been shown to normalize menstrual cycles. Exhibit 1 at 5-6. The beneficial effects of calcium on the menstrual cycle may prevent the development of PMDD and POS, respectively. Human clinical trials and other scientific evidence are discussed in detail in Exhibit 1 and are summarized in the following section.

2. Scientific evidence demonstrates the public health benefits of calcium

PMDD

PMDD and PMS include a broad range of clinical symptoms that may be related to vascular and smooth muscle responsiveness or to hormonal secretion. Exhibi 1 at 5. Calcium has been shown to play a role in neurotransmitter release and the release of endocrine and

exocrine products. Id. Calcium aids in the contraction of skeletal and smooth muscle. It has also been shown to play a role in metabolism in all tissues. Id. Some preliminary data has indicated a menstrual cyclicity of calcium-regulating hormones including serum parathyroid hormone and calcitonin. Id. However, the exact role of calcium in the physiology of PMS and PMDD is not known. Id. It is hypothesized that calcium coupled with hormones may modulate the feedback mechanisms that translate neuroendocrine and hormonal messages into the behavioral, mood, and somatic changes seen in PMS and PMDD. Id.

Phase-related changes in ionic calcium and the calcium-regulating hormones (serum calcitonin and plasma parathyroid hormone) have been measured in normally menstruating women. Id. Changes in calcium saliva levels in women with normal cycles have also been observed, apparently independent of calcium intake. Id. Finally, serum calcium concentrations were found to be significantly elevated during menstruation in women with normal cycles and in those with anovulatory cycles. Id. Women with anovulatory cycles also showed elevated calcium concentrations during the premenstrual phase. Id.

Two placebo-controlled randomized clinical trials confirm the association between chronic calcium deficiency and premenstrual dysphoric disorder. Exhibit 1 at 5. Placebo was ineffective in those trials. Id. The participants were supplemented with either 100 mg or 1200 mg of calcium daily for three months and experienced significant reductions in PMS and PMDD symptoms. In a similar study of *women with normal menstrual cycles* a diet providing 1336 mg of calcium daily decreased PMS and PMDD symptoms more significantly than a diet providing 587 mg of calcium daily. Exhibit 1 at 5.

Moreover, in 1999 a review of published clinical trials of calcium supplementation and PMS concluded that "calcium supplementation of 1200 to 1600 mg/day, unless contraindicated,

should be considered a sound treatment option in women who experience premenstrual syndrome." Similarly, the 2001 PDR for Nutritional Supplements states that calcium "may diminish some of the symptoms of premenstrual syndrome." Exhibit 2 at 75. Finally, DHHS' Office on Women's Health 4Women publication recommends a calcium supplement with vitamin D to "help with PMS symptoms." Exhibit 4 at 2.

POS

Animal studies have established calcium's role in oocyte activation and maturation resulting in the resumption and progression of follicular development. Exhibit 1 at 6. The role of calcium in oocyte differentiation and maturation in mammals is suggested by numerous animal investigations. Id. Changes in intracellular calcium regulate maturation of the immature oocyte and the activation and fertilization of the mature egg. Id.

Calcium's importance in oocyte activation and maturation supports the hypothesis that abnormalities in calcium homeostasis may underlie the pathogenesis of POS. Id. Calcium disregulation could be responsible for follicular arrest that manifests in the reproductive and menstrual disorders characterizing POS. Id. A six month human clinical trial on thirteen premenopausal women with POS daily supplementing with 1500 mg of elemental calcium as calcium carbonate, plus sufficient vitamin D to maintain serum concentrations within a certain range to aid in calcium absorption, normalized menstrual cycles (in seven of the nine participants who did not have regular menstrual cycles prior to the study) and restored fertility as evidenced by pregnancy in two of the participants. Id.

Thus, the evidence shows that there is significant scientific agreement that calcium reduces the risk of PMDD and POS thus providing a public health benefit.

3. Scientific Summary Issues

a. Is there an optimum level of the particular substance to be consumed beyond which no benefit would be expected?

Clinical trials have tested daily doses up to 8000 mg of calcium carbonate (up to 3200 mg of elemental calcium) in adults with renal failure, 7800 mg of calcium carbonate and 5200 mg of elemental calcium in young men and women and 3240 mg of calcium carbonate in healthy premenopausal women. Exh. 1 at 7. The clinical trials reveal an absolute lack of evidence of clinically-significant reactions that could be attributed to dietary calcium. Id. at 7. Moreover, there are no reports of overdosage. Exh. 2 at 77.

A lowest-observed-adverse-effect level (LOAEL) for calcium in the range of 4 to 5 grams with an uncertainty factor of 2 has been identified for adults, according to the PDR (citing the Food and Nutrition Board of the Institute of Medicine). Id. at 78. Based on that information the tolerable upper intake level for children (1-18 years) and adults (including during pregnancy and lactation) is 2,500 mg/day. Id; See also, Exh. 1 at 8. The attached scientific report states that reliable and credible scientific literature indicates that daily dietary supplementation of calcium of at least 1200 mg/day of elemental calcium is effective in reducing the risk of cyclic severe depression associated with the menstrual cycle, PMDD, the onset of symptoms of PMDD, abnormal menstrual cycles, and POS. Id. at 9.

b. Is there any level at which an adverse effect from the substance or from foods containing the substance occurs for any segment of the population?

There is no increased risk for nephrolithiasis among individuals who consume recommended amounts of calcium. See Exhibit 1 at 8 and the Petitioner's simultaneously filed health claims for calcium and kidney stones (hereinafter "Calcium/Kidney Stone Petition") for further discussion of studies on point. The LOAEL for calcium for individuals with a history of nephrolithiasis was calculated to be 1685 mg daily, an amount less than recommendations. Id.

FDA has concluded that daily intakes of elemental calcium up to 1800 mg pose no increased risk for kidney stones among the general population. Id. citing 58 FR 2665.

By contrast the PDR states that supplemental calcium taken without food may increase the risk of kidney stones in women and men. Exhibit 2 at 76. The theory is that taking calcium supplements without food limits the opportunity for the beneficial effect that calcium may have in binding oxalate in the intestine. Id. The Calcium/Kidney Stone Petition reveals that theory to be incorrect.

The PDR states "calcium supplements are generally well tolerated." Exhibit 2 at 77. For calcium carbonate, it states that its use may cause gastrointestinal side reactions as constipation, bloating, gas, and flatulence. Id. Prolonged use of doses of calcium carbonate in excess of 12g daily (about 5g of elemental calcium) may lead to milk-alkali syndrome, nephrocalcinosis, and renal insufficiency. Id.

c. Are there certain populations that must receive special consideration?

The PDR for Nutritional Supplements states that persons who form calcium-containing kidney stones are advised against taking supplemental calcium. Id. at 77. Persons with achlorhydria should take calcium carbonate with food. Id. Calcium supplementation is contraindicated in persons with hypercalcemia (hypercalcemia is caused by sarcoidosis, hyperparathyroidism, hypervitaminosis D, and cancer). Id. at 76. However only with daily intakes of over 4,000 mg of calcium may there be an increased risk for the development of hypercalcemia, particularly if accompanied by equivalently large amounts (over 6,000 mg) of carbonate. Exh. 1 at 7-8.

Conditions that produce lower levels of circulating estrogen alter calcium homeostasis. The 1997 DRI Chapter on calcium states that young women with amenorrhea resulting from

anorexia nervosa have reduced net calcium absorption, higher urinary calcium excretion, and a lower rate of bone formation. Exh. 3 at 76. Exercise-induced amenorrhea also results in reduced calcium retention and lower bone mass. Id.

d. What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?

According to the PDR, concomitant use of calcium with biophosphonates, levothyroxine (only calcium carbonate), quinolones, and tetracycline may decrease absorption of those drugs. Exh. 2 at 77. Concomitant use of calcium with H2 blockers and proton pump inhibitors may decrease absorption of calcium. Id. Concomitant use with vitamin D analogues may increase absorption of calcium. Id.

4. Potential effect of the use of the proposed claims on food consumption, including significant alterations in eating habits and corresponding changes in nutrient intakes.

Daily calcium consumption meets or exceeds the RDI only in a small fraction of the population. Exh. 1 at 6. Only half of children 4 to 8 years old consume at least 800 mg of calcium daily; less than 25% of boys 9 to 13 years old consume at least 1300 mg of calcium daily; less than 50% of boys 14 to 18 years old consume at least 1300 mg of calcium daily; only about 5% of adolescent girls consume at least 1300 mg of calcium daily; less than 50% of adult men and only about 10% of adult women consume at least 1000 mg of calcium daily; and less than 10% of the population over 50 years old consumes at lease 1200 mg of calcium daily. Id. The Institute of Medicine has suggested that "some seemingly healthy individuals may require higher calcium intakes" and that for individuals at risk for dietary calcium intakes below recommendations, "use of calcium supplements may be desirable in order to meet [recommendations]." Exhibit 1 at 6-7. The PDR for Nutritional Supplements states that about 25% of women in the U.S. take calcium supplements. Id. at 74.

The proposed claims may increase use of oral calcium supplements among the general population, including female populations at risk of PMDD and POS. The Petitioner does not anticipate substantial dietary changes in the general population but does expect there to be some increase in consumer preferences for calcium-containing supplements. The effect on such people is expected to be beneficial, reducing the risk of those diseases and health conditions.

5. Prevalence of the disease or health-related condition in the U.S. population and the relevance of the claims in the context of the total daily diet.

Eighty percent of women are estimated to experience PMS, 40% of women (half of those experiencing PMS) experience symptoms sufficient to affect their daily lives, and 3% to 8% experience PMDD. Exhibit 1 at 4. POS affects 6% to 10% of reproductive-aged women. Id. at 5. At least 30% of women have some symptoms of POS. Exhibit 5 at 1. POS is the leading cause of infertility and is the most common reproductive syndrome in women of childbearing age. Id.

As stated above in the preceding section, daily calcium consumption meets or exceeds the RDI in only a small fraction of the US population. Exhibit 1 at 6. In the context of the daily diet supplementation represents the most efficient method for the population to meet the RDI and the best calcium source for consumers to avoid the high fat content of dairy sources. Moreover, claims appearing at the point of sale are best able to guide consumers in making health enhancing ingestion decisions.

6. Calcium conforms to the definition of the term "substance" in 21 C.F.R. §101.14(a)(2).

"Substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances." 21 C.F.R. §101.14(a). Calcium is a substance within the

meaning of Section 101.14(a). Calcium is an essential mineral and an alkaline earth metal. Exhibit 2 at 74. Calcium accounts for one to two percent of adult human body weight. Exhibit 3 at 71 and Exhibit 2 at 74. It is a major constituent of bones and teeth where 99% of total body calcium is present. Exhibit 2 at 74 and Exhibit 3 at 71. The remainder of body calcium is present in blood, extracellular fluid, muscle, and other tissues where it plays a role in mediating vascular contraction and vasodilation, muscle contraction, the beating of the heart, blood coagulation, the production of energy, maintenance of immune function, nerve transmission, and glandular secretion. Id. Milk products such as milk and cheese are the most calcium-dense foods and are the major food sources of calcium in North American diets. Exhibit 3 at 73. However, as discussed in the Glade Report attached to the petition concerning calcium and its relationship to cancer submitted simultaneously with this one, the fat in dairy products may increase the risk of cancer. Id. at 30; 31. Other foods rich in calcium include collard greens, Chinese cabbage, mustard greens, broccoli, bok choy, tofu, and sardines with bones. Exhibit 2 at 74 and Exhibit 3 at 73. Grains and beans (particularly soybeans) are also sources of calcium. Exhibit 3 at 73. One source of calcium used in manufacturing supplements is calcium from coral which contains both calcium carbonate and calcium oxide.

Calcium supplements are available in several different salts, dosage forms, and dosage amounts. Calcium supplements include the salts calcium carbonate, calcium citrate, calcium phosphate, calcium lactate, and calcium gluconate. Exhibit 2 at 77. Dosage forms include capsules, chewable tablets, liquids, powders, suspensions, tablets and wafers. Exhibit 2 at 78. Dosage amounts range from 150 mg (capsule) to 1.8 G/5ml (syrup) with typical tablets and capsules having 250 or 500 mg amounts. Id.

C. Analytical Data

The amount of calcium contained in dietary supplements that bear the petitioner's health claims may be ascertained by the same methods used by FDA to determine the amount of calcium contained in dietary supplements bearing the calcium and osteoporosis health claim approved in 21 C.F.R. § 101.72. That section and the final rule implementing that regulation do not identify the analytical method for that determination. See, 21 C.F.R. § 101.72 and 58 FR 2665. According to the Association of Analytical Chemists (AOAC), the amount of calcium contained in a dietary supplement that may be a candidate for bearing the health claims can be ascertained by the method attached as Exhibit 6.

D. Model Health Claims

Petitioner proposes the following model claims for calcium:

Calcium may reduce the risk of cyclic severe depression associated with the menstrual cycle.

Calcium may reduce the risk of premenstrual dysphoric disorder.

Calcium may reduce the risk of the onset of symptoms of premenstrual dysphoric disorder.

Calcium may reduce the risk of abnormal menstrual cycles.

Calcium may reduce the risk of polycystic ovary syndrome.

Multiple studies have shown that oral supplementation with calcium significantly reduces risk of the above diseases. Moreover, clinical trials and a long history of daily use have proven the safety of calcium supplements for the general population.

E. Attachments

Attached are copies of the scientific studies (Exhibit 1) and other information referenced in, and constituting the basis for, this Petition. To the best of Petitioner's knowledge, all non-clinical studies relied upon were conducted in compliance with the good laboratory practices regulations in 21 C.F.R. Part 58, and all clinical or other human investigations relied upon were either conducted in accordance with the requirements for institutional review at 21 C.F.R. Part 56 or were not subject to such requirements in accordance with 21 C.F.R. § 56.104 or 56.105, and were conducted in conformance with the requirements for informed consent in 21 C.F.R. § 50 et seq. See generally, 21 C.F.R. § 101.7 (c)-(d).

F. Exclusion from Environmental Assessment

The requested health claim approvals sought in this petition are categorically excluded from the environmental impact statement requirements under 21 C.F.R. § 25.24.

G. Conclusion and Certification

For the foregoing reasons, the Petitioner requests that FDA approve the proposed health claims. The Petitioner looks forward to working with FDA in promulgating a regulation authorizing the use of dietary supplement health claims concerning the association of calcium with: (1) cyclic severe depression associated with the menstrual cycle, (2) PMDD, (3) the onset of symptoms of PMDD, (4) abnormal menstrual cycles, and (5) POS.

Any questions concerning this Petition may be directed to Jonathan W. Emord, Esq., Emord & Associates, P.C. See below for his contact information. The undersigned certify on behalf of the Petitioner that to the best of the Petitioner's knowledge this petition is a representative and balanced submission that includes unfavorable information as well as favorable information, known to it to be pertinent to the evaluation of the proposed health claims.

Respectfully submitted,

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